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Idiopathic interstitial pneumonias

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A B S T R A C T

Idiopathic interstitial pneumonias are diseases of the lung interstitium where the etiology is unknown. They constitute the largest group of interstitial lung diseases. Making a diagnosis can be challenging due to the diversity of clinical presentations and frequently, non-specific radiological and pathological findings. The most common form, idiopathic pulmonary fibrosis, has a poor prognosis with median survival of 3 years from diagnosis. There have been changes in the nomenclature of different individual entities over the years. Moreover, there is paucity of data on the best treatments available to manage this group of lung diseases. The nomenclature, clinical features, pathophysiology, diagnostic techniques, and prognosis of the idiopathic interstitial pneumonias are discussed in this review.

Educational objectives

- To understand the nomenclature of the idiopathic interstitial pneumonias (IIPs).
- To review the pathophysiology and clinical features of IIPs.
- To illustrate the importance of high resolution computed tomography (HRCT), transbronchial lung biopsy (TBB) and video assisted thoracoscopic surgical (VATS) biopsy in the diagnosis of this group of lung diseases.
- To evaluate the diagnostic utility of bronchoalveolar lavage (BAL) in diagnosing different IIPs.
- To discuss the prognosis of IIPs.

1. Introduction

Idiopathic interstitial pneumonias (IIPs) are a diverse group of diseases of the lung parenchyma with variable prognoses. Despite advancements in diagnostic techniques and improvement in diagnostic yield, there has been little success in improving overall survival. Historically, there have been several different classifications such as those proposed by Liebow and Carrington[1] (1969), Müller and Colby[2] (1997), and Katzenstein[3] (1997). The most recent and comprehensive update on nomenclature has been the ATS/ERS international multidisciplinary consensus classification[4] (Fig. 1). It defines certain histologic patterns which form the basis for clinico–radiologic–pathologic diagnosis of individual entities of IIPs.

2. Usual interstitial pneumonia (UIP)/idiopathic pulmonary fibrosis (IPF)

Usual interstitial pneumonia (UIP) is the histological counterpart of idiopathic pulmonary fibrosis (IPF), which has also been called cryptogenic fibrosing alveolitis (CFA) in the UK and Europe. This disease has an estimated prevalence of 14–43 per 100,000 and an estimated yearly incidence of 7–16 per 100,000.[5] It is the most common form of IIP and carries the worst prognosis. Smoking has been associated with IPF but the exact association between smoking and clinical outcome in IPF is not absolutely clear. Recently a retrospective study[6] suggested that smokers have milder disease as compared to ex-smokers, but survival is better in non-smokers with IPF when compared to former smokers or combined group of former and current smokers.

The usual clinical presentation of IPF is with insidious onset of breathlessness, fine basal crackles on lung auscultation, type 1 respiratory failure, and a restrictive ventilatory defect. The clinical course is often slowly progressive leading to death after several years, but some patients may remain stable for many years until an "exacerbation" or an accelerated phase ensues with a rapid deterioration which is frequently fatal.

The chest radiograph (Fig. 2a) typically shows diffuse lower zone reticular opacities with volume loss. Advancement in the image quality and refinement of HRCT slices have made a great impact on our understanding of IPF on radiological grounds, and HRCT scan (Fig. 2b) is more sensitive than chest radiography in diagnosing early IPF. Typically there are areas of bilateral peripheral and subpleural reticular abnormalities without significant ground glass shadowing. Areas of honeycombing with traction bronchiectasis are in a basal distribution initially, which progresses to involve all lobes in later stages. In the presence of extensive ground glass

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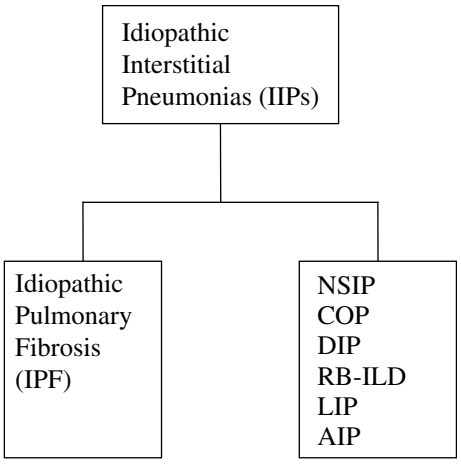

Fig. 1. Classification of idiopathic interstitial pneumonias. NSIP non-specific interstitial pneumonia; COP cryptogenic organising pneumonia; DIP desquamative interstitial pneumonia; RB-ILD respiratory bronchiolitis interstitial lung disease; LIP lymphoid interstitial pneumonia; and AIP acute interstitial pneumonia.

changes, alternative diagnoses must be considered and significant effort should be made to obtain histology.

Pulmonary function tests demonstrate a restrictive ventilatory defect with reduced gas transfer. The lung volumes are usually small but there may be mixed picture of obstructive and restrictive impairment in the presence of co-existing emphysema. PFTs are helpful in determining disease severity and hence prognosis at presentation, with a Tlco $<$ 40% predicted or desaturation during a six-minute walk indicating severe disease. Serial PFTs are the best way of monitoring changes in IPF, a $>$10% fall in FVC being a reliable indicator of disease progression.

Histologically, UIP manifests as heterogeneous areas of fibrosis, architectural distortion and honeycombing with minimal interstitial inflammatory changes. Characteristically, there are patches of fibroblasts, myofibroblasts and newly formed collagen, called fibroblastic foci (Fig. 2c) seen on histology. There is recent evidence that these fibroblastic foci are in fact part of a complex architecture which is highly interconnected and extends from pleura to the underlying lung parenchyma, reflecting a reactive process in UIP.[7]

3. Acute exacerbation of IPF (AE-IPF)

In 1993, Kondoh et al.[8] described 3 cases of IPF with acute clinical deterioration and progressive hypoxia. There were no identifiable infecting agents. Subsequently, acute exacerbation of IPF has been increasingly recognised although the precise incidence is unknown. The criteria[9] used for the diagnosis of AE-IPF have been refined and include (1) acute worsening of dyspnea over less than a month's duration (2) new pulmonary infiltrates on chest radiograph or CT scan (3) worsening hypoxemia and (4) absence of an identifiable cause including infection or cardiovascular disease. HRCT scan typically shows diffuse ground glass change superimposed on background peripheral reticulation and/or honeycombing consistent with UIP. It can be challenging to differentiate AE-IPF from infection as the clinico-radiological features do overlap and many patients receive broad-spectrum antibiotics for presumed bacterial pneumonia. This diagnosis is particularly challenging in patients without a prior diagnosis of IPF, when respiratory failure makes bronchoscopy, BAL or lung biopsy difficult or impossible. If histology is obtained, the most common histological pattern is diffuse alveolar damage on an underlying UIP pattern. However, organising pneumonia has been reported with a favourable response to corticosteroids.[10]

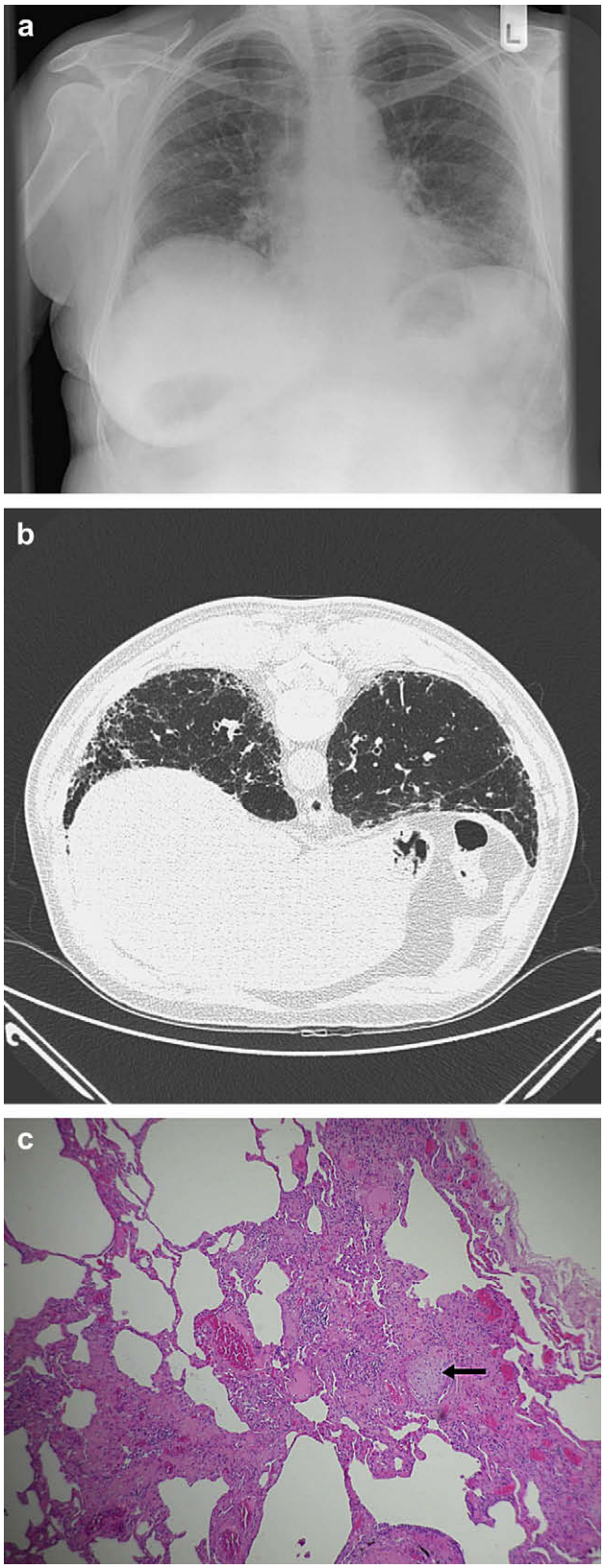

Fig. 2. (a) Chest radiograph showing diffuse interstitial infiltrates in IPF. (b) HRCT scan demonstrating subpleural reticulation with honeycombing without significant ground glass change, highly suggestive of usual interstitial pneumonia (UIP). (c) Lung biopsy showing heterogeneous areas of architectural distortion with fibrosis and fibroblastic foci (arrow) along with normal lung parenchyma consistent with usual interstitial pneumonia (UIP).

4. Pathogenesis of idiopathic pulmonary fibrosis

Many different mechanisms have been proposed to try to explain the pathophysiology of IPF. Historically, IPF was believed to be an inflammatory disorder but this hypothesis has been challenged for a number of reasons. First, inflammation is not a prominent histopathologic finding. Second, IPF does not respond well (or at all) to anti-inflammatory treatment in the form of corticosteroids or other immunosuppressives. Third, epithelial injury can lead to pulmonary fibrosis even in the absence of significant ongoing inflammation.[11] It is now widely believed that injury to the alveolar epithelial cells is the first insult in the pathogenesis of IPF, but the exact nature of the cellular injury has yet to be identified. However, epithelial injury may by immunological (either antibody or cell-mediated), chemical (e.g., reflux of gastric contents), microbial, or particulate (organic or inorganic). There is evidence to support each of these possibilities, which has been reviewed elsewhere. Transformation of epithelial cells into fibroblasts [epithelial mesenchymal transition (EMT)] is an attractive explanation for the preponderance of fibroblasts in the lung in IPF. Production and activation of the pro-fibrotic cytokine TGF-ß are thought to be a cardinal feature in pulmonary fibrosis.[12] Activation of protease activated receptors by the coagulation cascade has also received much attention as a driver of fibroblast proliferation and activation.[13]

There has been much interest in how certain genetic differences might predispose to IPF. For example, we have shown that the NA1/NA2 polymorphism of the IgG receptor CD16B is associated with IPF, supporting a role for an underlying immunological insult (Bournazos et al., submitted). Gene expression profiling has shown that there are clearly different gene signatures in IPF patients compared to normal controls. Zuo and co-workers[14] found that the genes encoding extracellular matrix formation and degradation were significantly increased in fibrotic lungs, the most distinctive being matrix metalloproteinase-7 (MMP-7). The only clearly defined genetic mutations in association with IPF are in the gene encoding surfactant protein C (*SFTPC*) and telomerase genes *hTERT* and *TERC*.[15–17] Selman and colleagues[18] looked at gene expression profiles of 114 patients with IPF and found that adenosine 2B receptor and prominin-1/CD133 genes were over expressed in the rapidly progressive variant. Moreover, it may be possible to distinguish between familial and idiopathic forms of idiopathic interstitial pneumonias on the basis of gene expression.[19]

5. Non-specific interstitial pneumonia (NSIP)

Non-specific interstitial pneumonia (NSIP) is a histological diagnosis. Despite its unfortunate name, idiopathic NSIP is regarded as a distinct disease entity characterized by homogenous lung fibrosis that has a better prognosis than IPF. In the 2002 ATS/ERS international multidisciplinary consensus classification,[4] idiopathic NSIP was classified as a provisional diagnosis rather than a specific disease entity. However, recently a report of American Thoracic Society project[20] concluded that idiopathic NSIP is a specific disease entity that occurs mostly in middle-aged women who are never-smokers. Here we focus on idiopathic NSIP, bearing in mind that the histological picture of NSIP may also be found in connective tissue diseases, HIV infection, drug reactions, and hypersensitivity pneumonitis.

The clinical presentation of NSIP is often with sub-acute onset of breathlessness. The chest radiograph (Fig. 3a) shows interstitial infiltrates while HRCT scan (Fig. 3b) typically shows areas of ground glass attenuation with or without significant honeycombing and the distribution of lung parenchymal involvement is rather more uniform than IPF. However, it can be extremely challenging to differentiate fibrotic NSIP from IPF on clinico-radiological grounds.

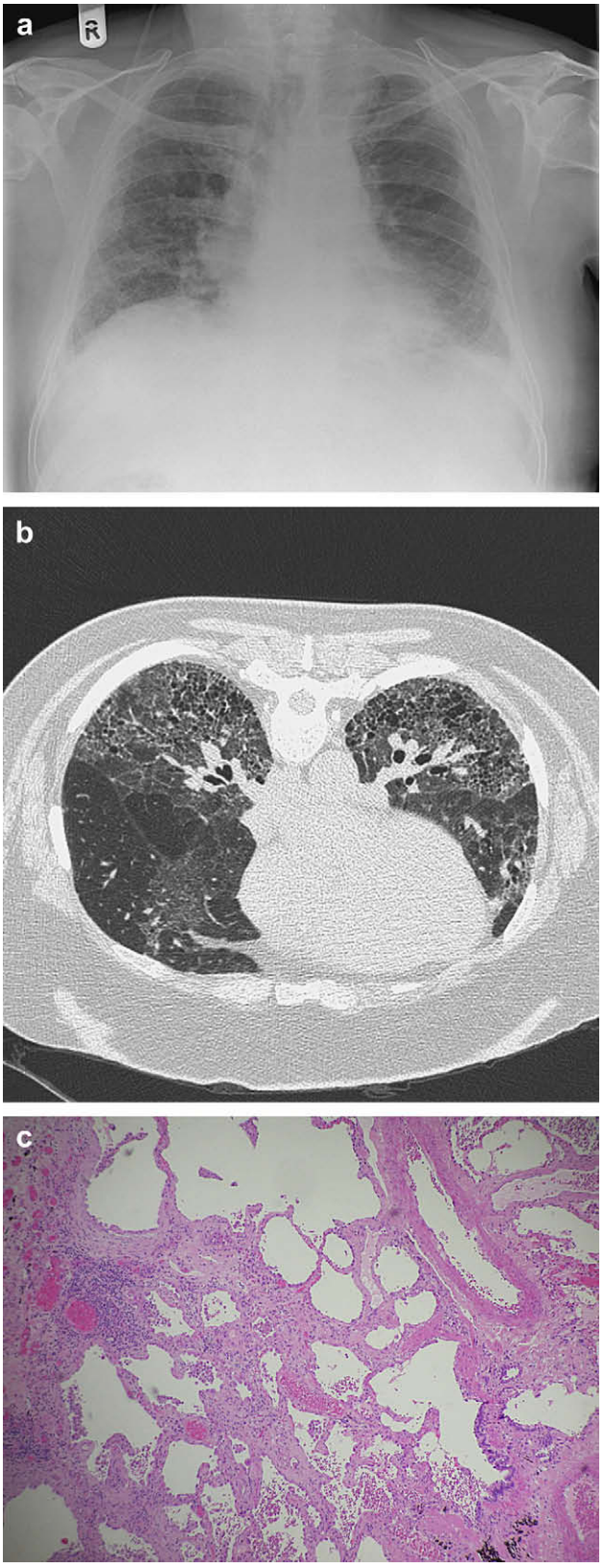

Fig. 3. (a) Chest radiograph showing bilateral reticulo-nodular shadowing in a patient with fibrotic NSIP. (b) HRCT scan showing diffuse involvement of lung parenchyma with bilateral honeycomb change and associated ground glass attenuation suggestive of fibrotic NSIP. (c) Diffuse areas of interstitial inflammation and fibrosis in a uniform pattern on histology, diagnostic of NSIP.

NSIP has been histologically subdivided into cellular, fibrotic and mixed patterns. Fibrotic NSIP is by far the most common, and is characterized by homogenous areas of interstitial fibrosis with minimal inflammation (Fig. 3c). Fibroblastic foci are an infrequent feature. Cellular NSIP is characterized by inflammatory infiltrate without fibrosis and has the best prognosis out of all three categories.

With regards to prognosis, NSIP has a better prognosis than UIP.[21–23] In view of significantly different clinical outcome, it is critical to obtain histological diagnosis when HRCT shows features suggestive of NSIP.

6. Cryptogenic organising pneumonia (COP)

Cryptogenic organising pneumonia is a distinct disease entity of unknown cause described by Davison and colleagues in 1983.[24] It is characterized by proliferation of granulation tissue in alveolar spaces and sometimes bronchioles. It has also been known as idiopathic bronchiolitis obliterans organising pneumonia (BOOP), a term which does not reflect the true histopathological pattern of organising pneumonia. BOOP is not a recommended terminology to be used for COP as bronchioles are not always involved and it can easily be confused with obliterative bronchiolitis (OB), which is a completely different disease.

COP usually presents with relatively short duration of dyspnea with dry or productive cough. Patients may have fever, sweats, weight loss and myalgia, and laboratory tests typically show increased CRP (C reactive protein), ESR (erythrocyte sedimentation rate) and peripheral blood neutrophilia.[25] The presenting features are often indistinguishable from lung infection, so patients are frequently treated with multiple courses of antibiotics, and the diagnosis of COP is raised when the pneumonia fails to resolve, or when it relapses.

COP can be subdivided into three variants according to prognosis. *Typical COP* is associated with good overall prognosis with spontaneous remission in about 50% of cases in most case series.[26–29] *Acute fulminant COP* presents with features of acute respiratory distress syndrome (ARDS) and frequently needs mechanical ventilatory support. This rare variant is occasionally fatal without progressing to overt fibrosis. The biopsy shows features typical of organising pneumonia. It might pose a challenge to distinguish it from acute interstitial pneumonia on clinical and radiological grounds. *Fibrosing COP* is a rare subset of COP where clinical outcome is variable. There is usually mild interstitial fibrosis which is non-progressive in nature. Moreover there is evidence that some cases might lead to rapid progression of respiratory failure and death as described by case series of 10 patients by Cohen and colleagues.[30]

The most common radiographic features are unilateral or bilateral areas of patchy consolidation (Fig. 4a). CT scan (Fig. 4b) typically shows areas of airspace consolidation[31,32] with air bronchograms. The distribution of parenchymal abnormality is usually peribronchial or subpleural with propensity to involve basal zones of the lung. There may be ground glass attenuation present in approximately 60% of cases with COP.[4]

The histology (Fig. 4c) shows patchy fibroblastic plugs within the alveoli, called Masson bodies. There is minimal architectural distortion and frequently, there is an associated inflammatory infiltrate with aggregates of foamy macrophages, but a paucity of honeycomb change or severe fibrosis. It must be emphasised that this histological appearance of organising pneumonia may occur in many other conditions, including bacterial and viral infection and in areas of other ILDs including UIP. A confident diagnosis of COP illustrates the importance of clinical and radiological findings in addition to histology, and particularly exclusion of infection.

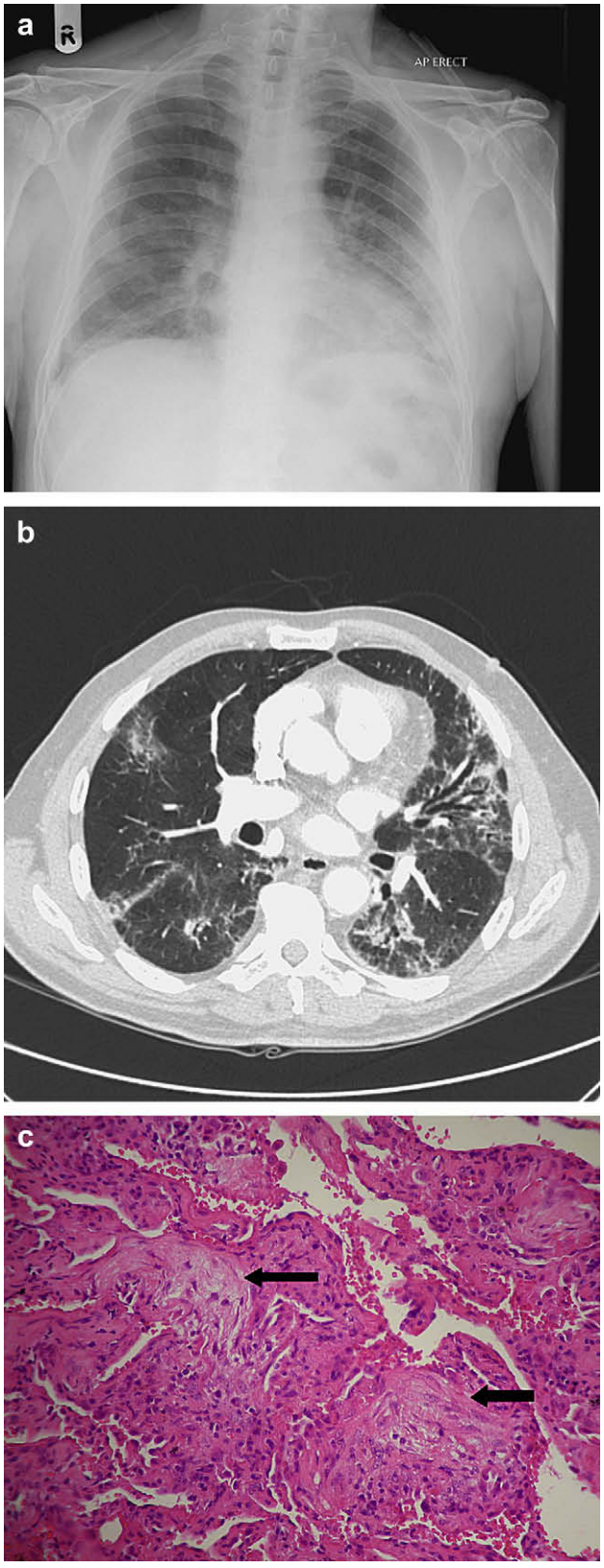

Fig. 4. (a) Bilateral patchy consolidation in lower zones on chest radiograph in cryptogenic organizing pneumonia (COP). (b) CT thorax depicting patchy areas of pulmonary infiltrates with associated bronchiectasis. The lung biopsy was suggestive of organizing pneumonia. (c) Histology from a patient with COP demonstrating Masson bodies (arrows) and inflammatory infiltrate with preservation of lung architecture.

7. Respiratory bronchiolitis interstitial lung disease (RB-ILD)

Respiratory bronchiolitis, first described in 1974 as a distinct histopathologic entity, is characterized by the presence of pigmented macrophages in respiratory bronchioles exclusively in cigarette smokers. It is almost always asymptomatic in all cases. A small proportion of patients with respiratory bronchiolitis develop a clinical entity called RB-ILD, which presents with symptoms of dyspnea and cough. The majority of cases have mild symptoms which are non-progressive. RB-ILD and DIP are believed to represent two ends of the same clinico-pathological spectrum as both conditions share many clinical and histological features. It typically affects males in their fourth or fifth decade with a smoking history of 30 pack-years or more.

The chest radiograph may show reticular or reticulo-nodular shadowing in a bibasal distribution. The CT scan reveals centrilobular nodule formation, bronchial wall thickening and occasionally ground glass attenuation. There is often centrilobular emphysema associated with these changes. Pulmonary function tests reveal mild to moderate reduction in gas transfer. There may be an isolated increase in residual volume[33] and mixed obstructive and restrictive ventilatory defects.

On histology, there is accumulation of pigmented brown macrophages in respiratory bronchioles, alveolar ducts and peribonchiolar alveolar spaces. A fairly confident diagnosis of RB-ILD can often be made on history and HRCT findings; hence a lung biopsy is not required in the majority of cases.

8. Desquamative interstitial pneumonia (DIP)

Desquamative interstitial pneumonia is a rare IIP, typically affecting smokers in their fourth or fifth decade of life. It was originally described by Liebow and colleagues[34] as they believed that there was desquamation of alveolar epithelial cells in this disease. However, it is now recognised that the histopathological hallmark is diffuse accumulation of pigmented macrophages in alveolar air spaces rather than desquamation of epithelium. A more accurate term would be 'alveolar macrophage pneumonia' but in view of rarity of this condition, the term DIP was retained in the ATS/ERS consensus classification.[4]

The chest radiograph is not very sensitive to detect DIP but may show widespread ground glass haziness (Fig. 5a). HRCT scan (Fig. 5b) typically reveals ground glass opacification with or without reticulation and honeycombing fairly similar to NSIP. There is lower zone predominance and the pattern of interstitial abnormalities is diffuse and uniform in contrast to UIP. Lung biopsy (Fig. 5c) shows presence of intra-alveolar macrophages and mild interstitial fibrosis with chronic inflammatory cell infiltrate. DIP is distinguished from RB-ILD by the lack of bronchiolocentric distribution. The prognosis of DIP is generally good, with 70% survival after 10 years.[35]

9. Lymphoid interstitial pneumonia (LIP)

Lymphoid interstitial pneumonia was the term originally used by Liebow and Carrington in 1966 to describe a histopathologic entity with diffuse lymphocytic infiltration of pulmonary interstitium. It can occur in association with connective tissue diseases, autoimmune diseases such as pernicious anaemia and chronic active hepatitis, HIV, and hypogammaglobulinemia, particularly common variable immune deficiency. Previously, it was considered to be a pre-malignant entity that transformed into lymphoma, but there is no robust evidence that LIP has a malignant potential; hence it is included in the classification of IIPs as a distinct entity. The pathogenesis of LIP is considered to be autoimmune in view of

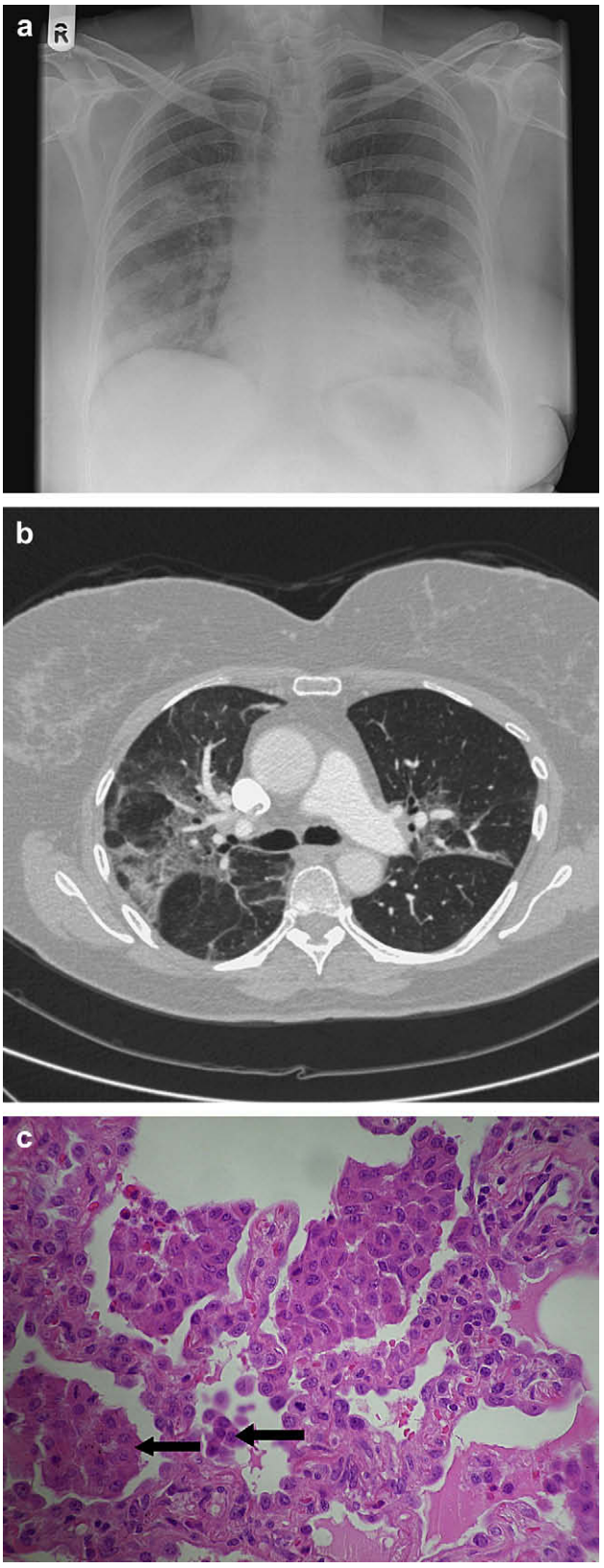

Fig. 5. (a) Chest radiograph with bilateral ground glass shadowing and ill-defined opacities. (b) HRCT showing extensive ground glass shadowing without honeycombing in a diffuse pattern affecting all lobes in DIP. (c) VATS biopsy showing evidence of accumulation of alveolar macrophages (arrows) with a focal inflammatory cell infiltrate and mild interstitial fibrosis, diagnostic of DIP.

Table 1
ATS/ERS criteria for diagnosis of IPF in the absence of surgical lung biopsy.

Major criteria	Minor criteria
Exclusion of known causes of ILD	Age > 50 years
Abnormal lung function tests showing restrictive ventilatory defect with impaired gas exchange	Insidious onset of otherwise unexplained dyspnea on exertion
Bibasal reticulation with minimal ground glass change on HRCT scan	Duration of illness > 3 months
Transbronchial lung biopsy or BAL showing no features to support an alternative diagnosis	Bibasal inspiratory crackles(dry or velcro type)

strong association with many autoimmune diseases such as Sjogren's syndrome. Moreover, there is a possibility of an infectious etiology as LIP is seen in association with EBV[36] (Epstein Barr virus), HIV and Human T-lymphotropic virus type I (HTLV-I).[37]

Clinically, it presents with gradual onset of breathlessness and cough with a female predominance of 2:1, usually in the 4–7th decade of life. HRCT scan reveals areas of ground glass shadowing with interstitial thickening and formation of cysts in perivascular regions. Honeycomb change is rare in LIP.

Surgical lung biopsy is required to confidently make the diagnosis and histology shows diffuse interstitial infiltration by lymphocytes, plasma cells and histiocytes with increase in macrophages and type 2 epithelial cell hyperplasia. The mortality in LIP has been reported to be 38% in two observational studies[38,39] consisting of 26 patients. In these small studies 25% of cases showed rapid improvement, 15% showed mild improvement, and 25% remained stable. The mortality in these studies was predominantly related to progression of fibrosis and infections complicating immunosuppressive therapy.

10. Acute interstitial pneumonia (AIP)

AIP was first described by Hamman and Rich in 1935 and presents as a rapidly progressive form of interstitial lung disease with type 1 respiratory failure. It is histologically characterized by diffuse alveolar damage and formation of hyaline membranes. Neutrophil mediated injury is believed to play an important part in pathogenesis of AIP. The clinical, radiological, and histological features are similar to the acute respiratory distress syndrome (ARDS), and AIP may be considered to be idiopathic ARDS.

AIP tends to occur in previously healthy individuals. There is fairly short history of dyspnea and associated cough and fever with bilateral radiological infiltrates on chest radiograph and CT scan. There are bilateral crackles and patients are severely hypoxemic despite supplemental oxygen. HRCT scan shows bilateral areas of ground glass shadowing and patchy airspace consolidation. Moreover, there may be traction bronchiectasis and extensive reticulation in later stages. Many cases need mechanical ventilation, and even with the ventilatory support the mortality is extremely high (>50%).

Table 2
Bronchoalveolar lavage findings in different idiopathic interstitial pneumonias.

Disease entity	Cellular profile	Other features
Idiopathic pulmonary fibrosis	Neutrophils +++ Lymphocytes + Eosinophils +	Neutrophils → disease extent Eosinophils → disease progressiveness
Cryptogenic organizing pneumonia	Neutrophils + Lymphocytes + Eosinophils +	Foamy macrophages ↓ CD4+/CD8 ratio
Non-specific interstitial pneumonia	Lymphocytes + Eosinophils +	Eosinophilia is associated with increased mortality in SSc related NSIP

11. Role of lung biopsy in the diagnosis of IIPs

Lung biopsy plays a key role in the diagnosis and management of IIPs. It may be in the form of a transbronchial (bronchoscopic) lung biopsy (TBLB), or surgical lung biopsy.

TBLB is performed through a flexible fiberoptic bronchoscope and has a limited role in the diagnosis of IIPs. The site for transbronchial biopsy is guided by HRCT scan and generally 4–6 biopsy samples are recommended.[40,41] The biopsies are taken from areas of radiological abnormality adjacent to normal lung and avoiding parts of the lung with honeycomb change. The lingula and right middle lobes tend to provide limited diagnostic information, so these areas should not be the preferred sites to biopsy. The main limitation of TBLB is the small size of specimens obtained leading to poor diagnostic yield in most IIPs.

In the majority of patients with IIPs, surgical lung biopsy is required if the diagnosis is not apparent on clinical and radiological grounds. It has an extremely good diagnostic yield of >90% with a low mortality.[42] The method of choice is video assisted thoracoscopic surgical (VATS) biopsy, which is a safe procedure without significant short-term mortality[43] and with a shorter hospital stay and reduced analgesic requirements when compared with open lung biopsy (OLB).[44] The main complications are post-operative pain and persistent air leak. A surgical lung biopsy can be especially valuable in distinguishing between UIP and fibrotic NSIP with an IPF-like clinical/radiological profile. Moreover, ATS/ERS criteria[45] (Table 1) are a useful means to diagnose IPF in the absence of surgical lung biopsy. The likelihood of correct diagnosis of IPF is increased in the presence of all major and at least 3 of the four minor criteria.

The decision to perform a surgical lung biopsy should be made after multidisciplinary (clinician/radiologist/surgeon/pathologist) consensus and a frank discussion with appropriately informed patient where the results of the biopsy would provide valuable diagnostic and prognostic information.

12. Role of bronchoalveolar lavage in the diagnosis of IIPs

There is limited data on the role of bronchoalveolar lavage (BAL) in the diagnosis and to determine prognosis and need for treatment in the different IIPs. Its utility is predominantly limited to a research tool to examine immune effector cells accumulating at the alveolar level. There are certain conditions where BAL may contribute important additional diagnostic information when combined with clinical features and HRCT findings. These include eosinophilic pneumonia, alveolar proteinosis,[46] opportunistic infection, and malignancy.

The most common cell types in BAL seen in different IIPs are summarised in Table 2.

13. Conclusion

In summary, idiopathic interstitial pneumonias pose a diagnostic challenge to pulmonologists, radiologists and pathologists. It is extremely important to have a multidisciplinary approach in diagnosing this group of interstitial lung diseases with variable prognoses. Lung biopsy provides valuable information in many cases and should be undertaken if clinico-radiological correlation is insufficient to make a confident diagnosis.

Conflicts of interests statement

None to declare for any author.

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Consent: Informed consent was obtained by the patients to publish radiological and pathological images in this review.

CME section

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Educational questions:

Answer the following questions:

1. Which one of the following is NOT a feature of idiopathic pulmonary fibrosis?
   a. Presence of fibroblastic foci on histology
   b. Heterogenous areas of architectural distortion
   c. Honeycombing with minimal ground glass change on HRCT
   d. Extensive ground glass shadowing and dense consolidation on HRCT
   e. Subpleural and peripheral distribution of abnormalities

2. Which one of these is a histological feature of desquamative interstitial pneumonia?
   a. Desquamation of alveolar epithelial cells
   b. Accumulation of alveolar macrophages
   c. Extensive fibrosis with honeycombing
   d. Hemosiderin pigment laden-macrophages brightly staining with Prussian blue
   e. Formation of hyaline membranes

3. Regarding the lung biopsy in idiopathic interstitial pneumonias, select the correct statement:
   a. Transbronchial biopsy is the biopsy of choice
   b. VATS biopsy has better diagnostic yield than open lung biopsy
   c. Lung biopsy always provides the unifying diagnosis in IIPs
   d. The suitable biopsy site should be guided by HRCT scan
   e. Lingula and middle lobe are the most suitable sites to biopsy

4. Which of the following is NOT true regarding acute interstitial pneumonia?
   a. Histology shows formation of hyaline membranes
   b. Neutrophil mediated injury plays no role in the pathogenesis
   c. It is also known as Hamman–Rich syndrome
   d. Mortality is in the range of 50–60% despite ventilatory support
   e. Idiopathic ARDS is synonymous with acute interstitial pneumonia

5. Select the statement which best applies to non-specific interstitial pneumonia:
   a. The prognosis is similar to IPF
   b. Ground glass attenuation with minimal fibrosis is the most common radiological finding in the cellular variant
   c. There is no known association of NSIP with connective tissue diseases
   d. A confident diagnosis can be made without lung biopsy
   e. It is predominantly seen in elderly males with significant history of smoking

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